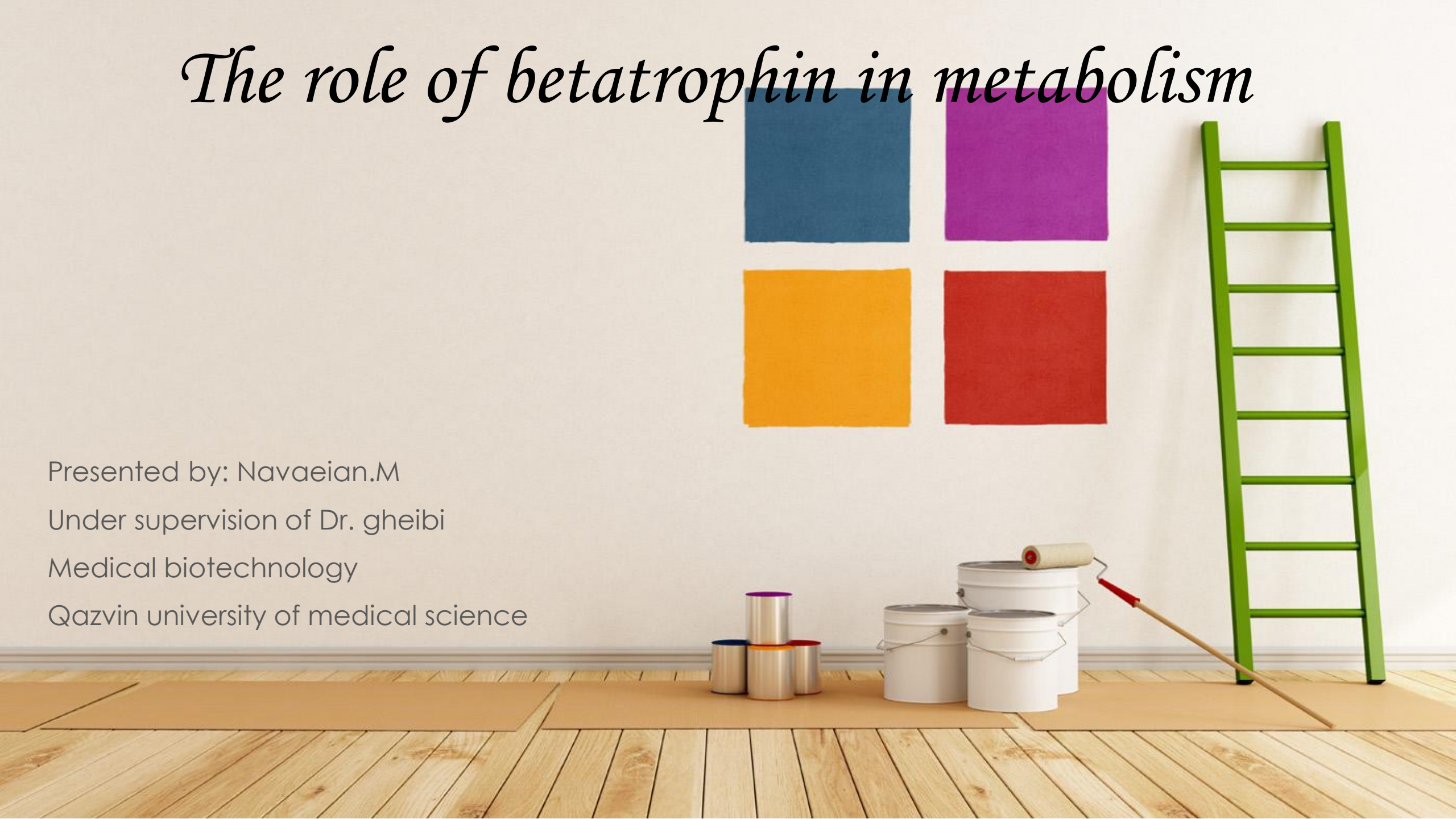
The role of betatrophin in metabolism



Presented by: Navaeian.M

Under supervision of Dr. gheibi

Medical biotechnology

Qazvin university of medical science

content


Introduction

Introduction

Betatrophin

- Angiopoietin-like protein 8 (ANGPTL8)
- C19ORF80
- lipasin
- RIFL
- TD26

- Gm6484 in mice

Atypical angiopoietin-like protein that regulates ANGPTL3

Fabiana Quagliarini[a,b,1], Yan Wang[a,b,c,1], Julia Kozlitina[a,b], Nick V. Grishin[c,d,e], Rhonda Hyde[a,b], Eric Boerwinkle[f], David M. Valenzuela[g], Andrew J. Murphy[g], Jonathan C. Cohen[a,b,2], and Helen H. Hobbs[a,b,c,2]

[a]Department of Internal Medicine, [b]Department of Molecular Genetics, [d]Department of Biophysics, and [e]Department of Biochemistry, [c]Howard Hughes Medical Research Institute, University of Texas Southwestern Medical Center, Dallas, TX 75390; [f]Division of Epidemiology School of Public Health, University of Texas, Houston, TX 77030; and [g]Regeneron Pharmaceuticals, Tarrytown, NY 10591

Contributed by Helen H. Hobbs, October 9, 2012 (sent for review August 27, 2012)

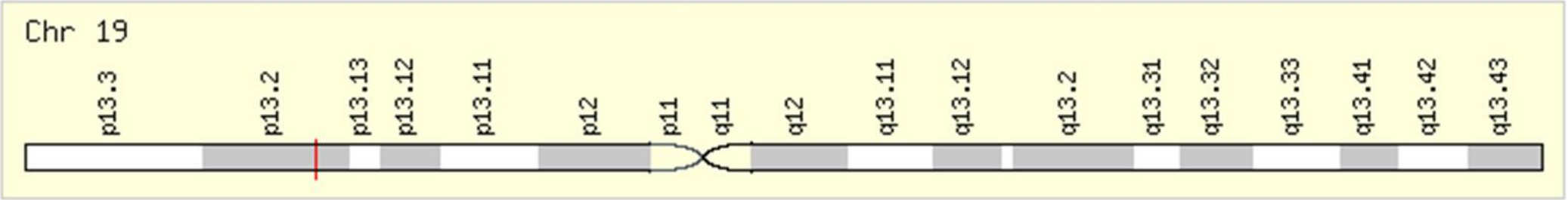
The angiopoietin-like (*ANGPTL*) genes encode a family of secreted proteins with pleiotropic effects on vascular cells (1), lipid metabolism (2), and stem cell biology (3). The family

Betatrophin

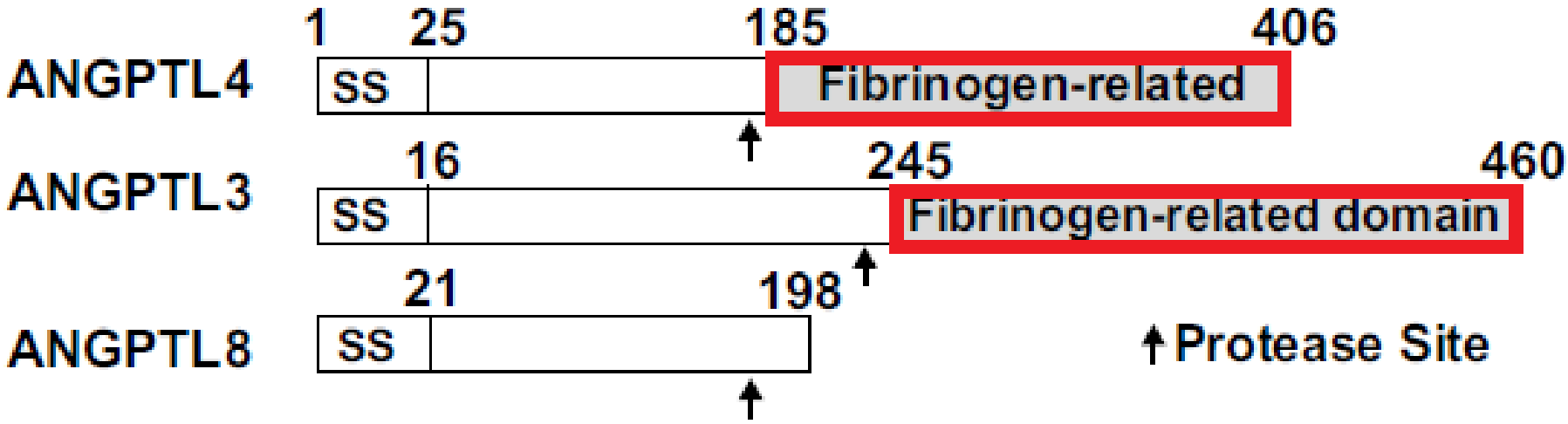
- is a novel but atypical ANGPTL family member
- promotes ANGPTL3 cleavage

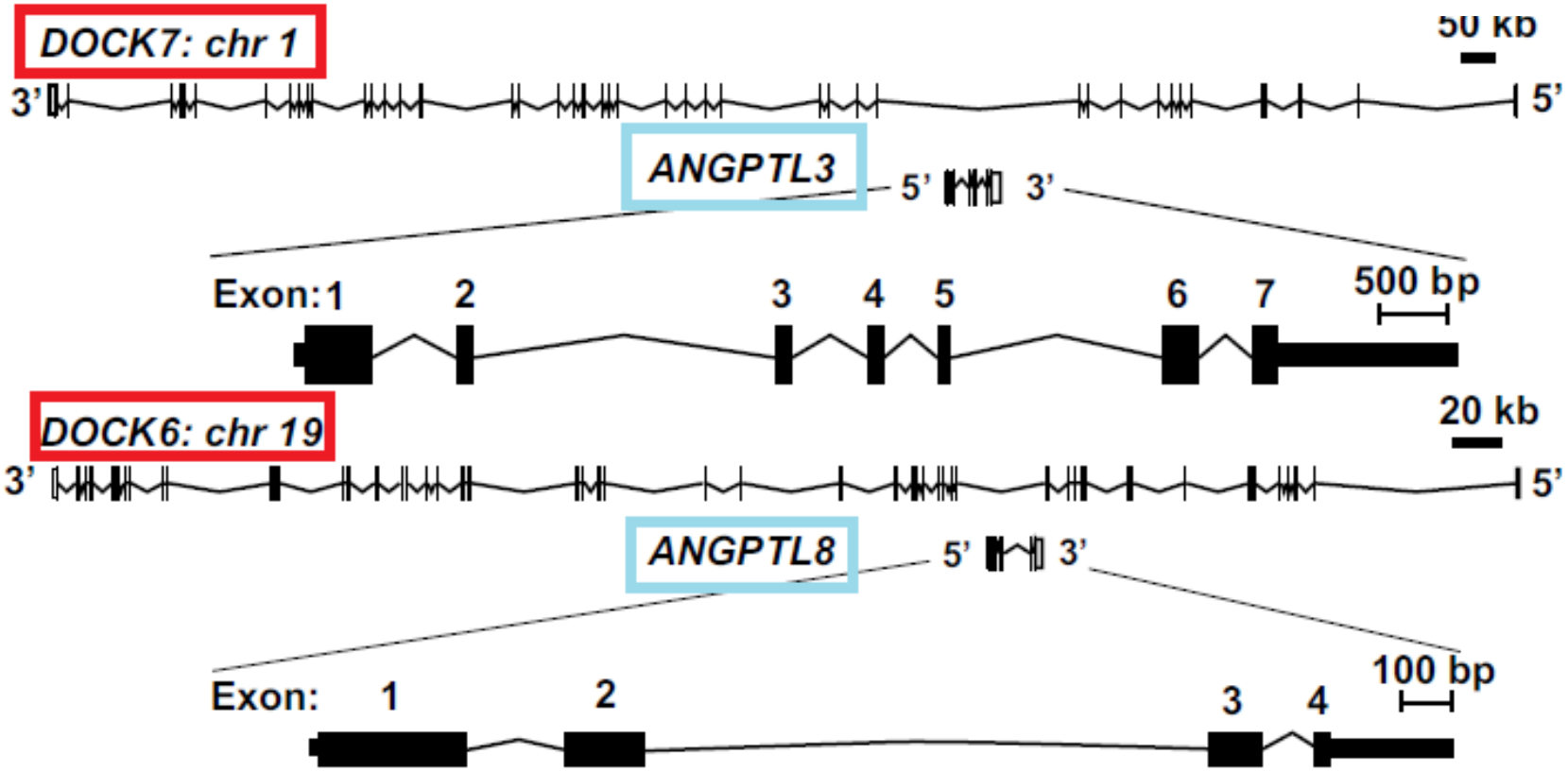
Cytogenetic band: 19p13.2 by Ensembl 19p13.2 by Entrez Gene 19p13.2 by HGNC

ANGPTL8 Gene in genomic location: bands according to Ensembl, locations according to GeneLoc (and/or Entrez Gene and/or Ensembl if different)



Introduction





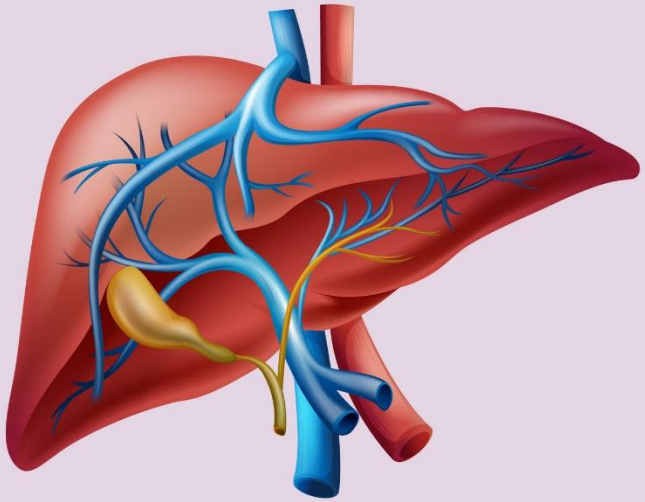
can be induced by tail vein injection. Of interest in this regard is ANGPTL3, which is structurally similar to ANGPTL8 and is located in the intron of a Dock gene as is ANGPTL8. Moreover, deletion or overexpression of ANGPTL3 and ANGPTL8 have similar effects on serum triglycerides

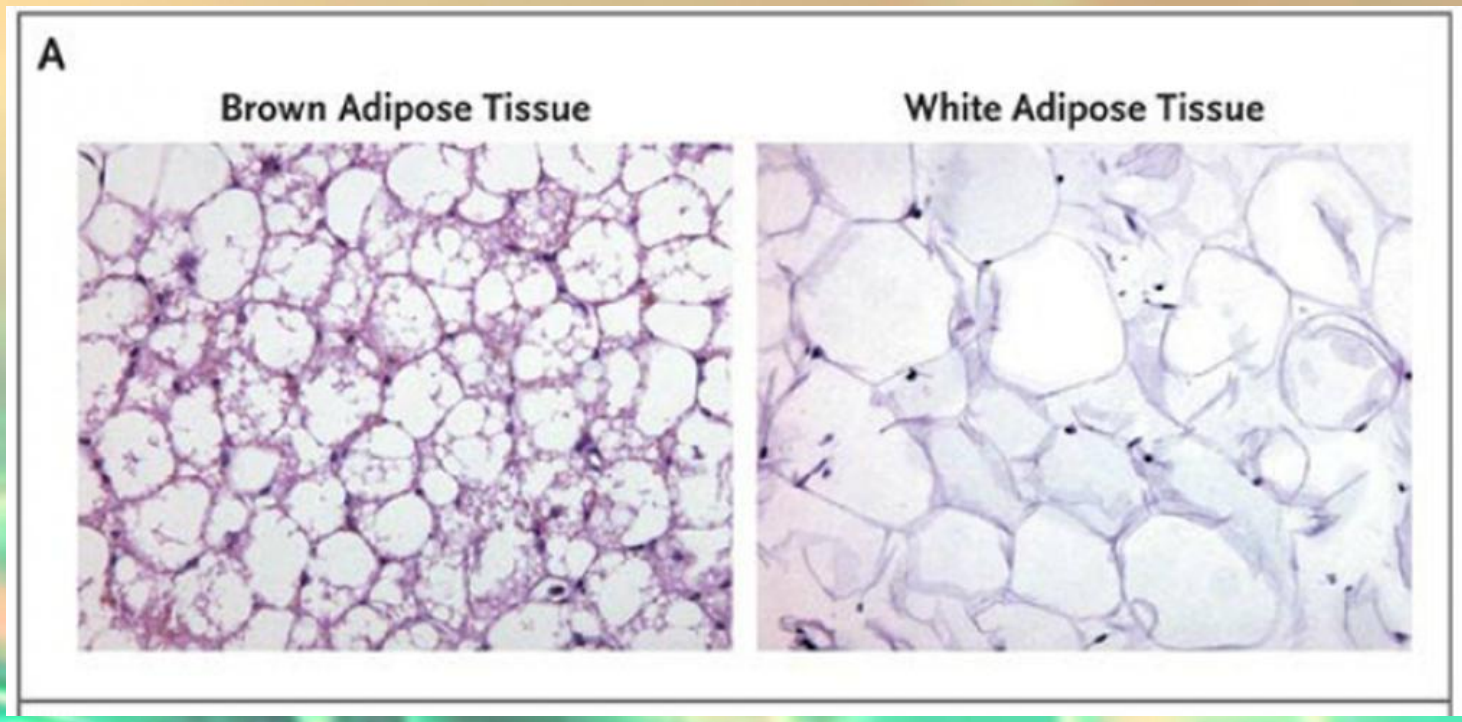
(78،49)

Introduction

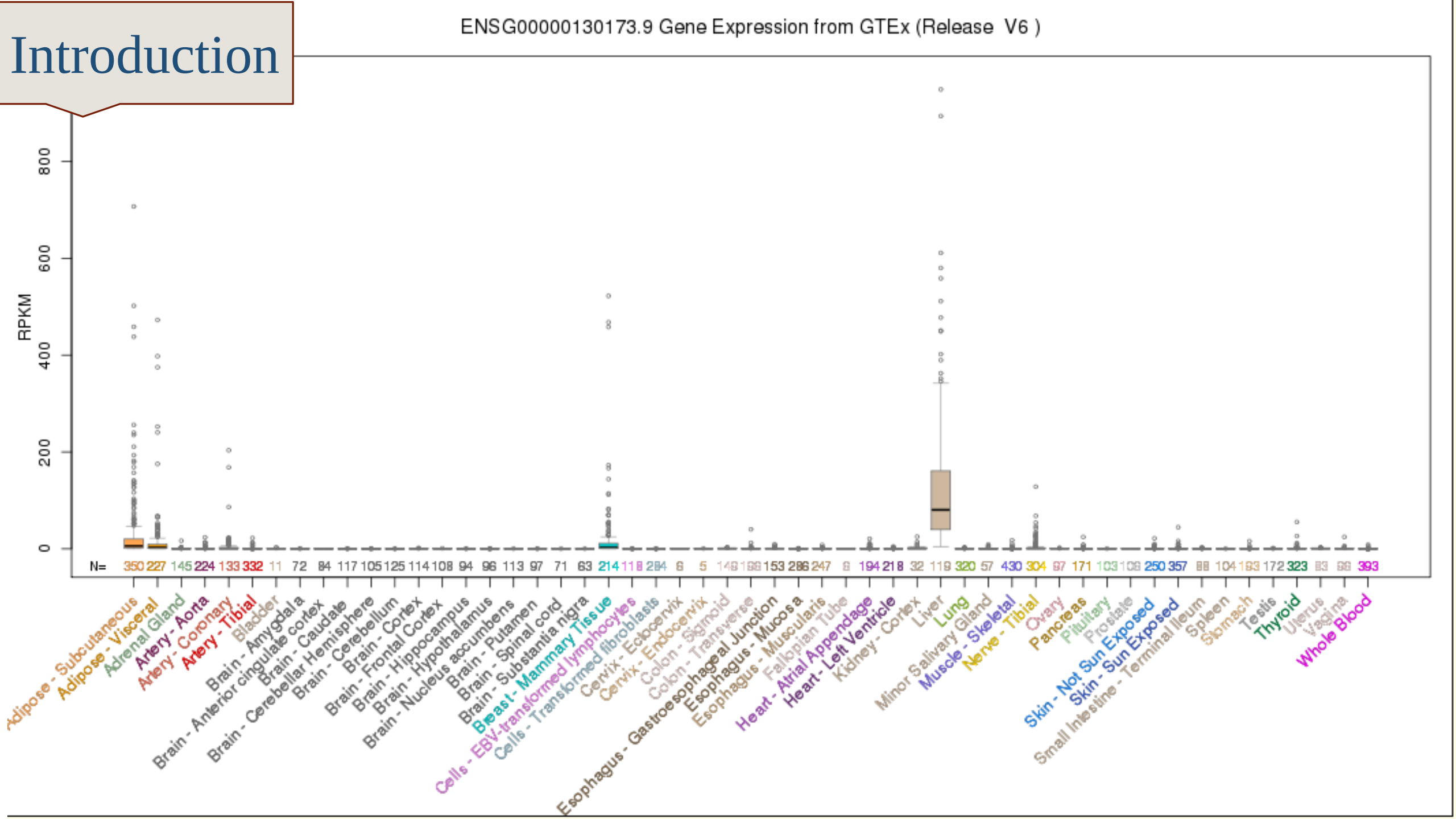
expressed :

- in liver
- white adipose
- brown adipose tissues





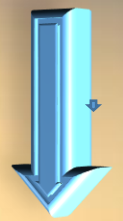
Introduction



Introduction

4 °C for 4 h

ANGPTL8



ANGPTL4 & ANGPTL2

Fasting

ANGPTL8

ANGPTL4

Introduction

High-fat diet

ANGPTL8

ANGPTL2

ANGPTL8 interaction with ANGPTL3 :

TG

β-cell proliferation

T1D

T2D

gestational diabetes mellitus

obesity

Hypothyroidism

MetS

polycystic ovary syndrome

ANGPTL8 & β-cell proliferation

Discussion

Betatrophin: a hormone that controls pancreatic β cell proliferation

Peng Yi[1], Ji-Sun Park[1] and Douglas A. Melton[1†]

[1]Department of Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Harvard University, 7 Divinity Avenue, Cambridge, Massachusetts, 02138, USA..

betatrophin induce pancreatic β cell proliferation, related to Figure 2 and

Figure 5. S961(10nMol/week) induced pancreatic β cell proliferation compared to vehicle shown by co-staining of the β-cell specific nuclear marker Nkx6.1 and Ki67 (**A**) or co-staining of insulin and PCNA (**B**).Expression of betatrophin in liver induces a dramatic pancreatic β cell proliferation increase compared to GFP

Elevated circulating lipasin/betatrophin in human type 2 diabetes and obesity

Zhiyao Fu[1]*, Feven Berhane[2]*, Alemu Fite[2], Berhane Seyoum[2], Abdul B. Abou-Samra[2,3] & Ren Zhang[1,2]

[1]Center for Molecular Medicine and Genetics, School of Medicine, Wayne State University, Detroit, MI 48201, USA, [2]Division of Endocrinology, School of Medicine, Wayne State University, Detroit, MI 48201, USA, [3]Department of Medicine, Hamad Medical Corporation, Doha, Qatar.

Lipasin (also known as C19ORF80, RIFL, ANGPTL8 and betatrophin) is a newly discovered circulating factor that regulates lipid metabolism and promotes pancreatic β-cell proliferation. Whether circulating

Our results showing that serum lipasin is increased in diabetes and that its levels are positively correlated with glucose levels suggest that glucose may play a role in regulating lipasin expression. It has been well established that in mice lipasin mRNA is induced by feeding[4,5,14]; this is consistent with the current observation, because feeding

In vivo targeted delivery of *ANGPTL8* gene for beta cell regeneration in rats

Jiaxi Chen · Shuyuan Chen · Pintong Huang · Xing-Li Meng · Sandra Clayton · Jin-Song Shen · Paul A. Grayburn

Received: 13 October 2014 / Accepted: 7 January 2015 / Published online: 28 February 2015

Abstract

Aims/hypothesis *ANGPTL8* is a circulatory hormone secreted from liver and adipose tissue that promotes pancreatic beta cell proliferation and interferes with triacylglycerol metabolism in mice. The clinical significance of its effects on induc-

ANGPTL8 gene therapy significantly alleviated but did not totally reverse STZ-induced diabetes in a rat model.

Conclusions/interpretation *ANGPTL8* induced adult and aged beta cell regeneration in a rat model.

Discussion

response to food intake.

Recently, Melton and his colleagues (13) reported that hepatic overexpression of ANGPTL8, which they called Betatrophin, promotes proliferation of pancreatic β-cells and increases insulin secretion. Thus, ANGPTL8 may also contribute to glucose homeostasis.

ANGPTL8/Betatrophin Does Not Control Pancreatic Beta Cell Expansion

Viktoria Gusarova,[1,*] Corey A. Alexa,[1] Erqian Na,[1] Panayiotis E. Stevis,[1] Yurong Xin,[1] Susan Bonner-Weir,[2] Jonathan C. Cohen,[3] Helen H. Hobbs,[4,5] Andrew J. Murphy,[1] George D. Yancopoulos,[1] and Jesper Gromada[1]

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[2]Joslin Diabetes Center, Harvard Medical School, Boston, MA 022
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http://dx.doi.org/10.1016/j.cell.2014.09.027

DISCUSSION

The main findings of the study are that (1) ANGPTL8 is not required for beta cell function or the compensatory beta cell growth response to insulin resistance, (2) overexpression of ANGPTL8 does not increase beta cell area nor improve glycemic control, and (3) ANGPTL8 regulates plasma triglyceride levels.

(60)

Angiopoietin-like protein 8 (ANGPTL8)/betatrophin overexpression does not increase beta cell proliferation in mice

Aaron R. Cox[1,2,3] · Carol J. Lam[1,2,3] · Claire W. Bonnyman[1,2,3] · Julia Chavez[1,2,3] · Jacqueline S. Rios[1,2,3] · Jake A. Kushner[1,2,3]

Received: 28 January 2015 / Accepted: 23 March 2015 / Published online: 28 April 2015

Results In two young and two aged cohorts of B6.129 mice, no substantial change in beta cell replication, mass or glucose homeostasis was observed following ANGPTL8 overexpression. Even in mice with extremely elevated *Angptl8*

Discussion

In conclusion, the role of ANGPTL8 in beta-cell proliferation in humans as well as mice has been challenged

2017 → 415 million adults

2040 → 640 million

ANGPTL8 & T1D

Increased circulating levels of betatrophin in individuals with long-standing type 1 diabetes

Daniel Espes · Joey Lau · Per-Ola Carlsson

Received: 9 July 2013 / Accepted: 13 September 2013 / Published online: 27 September 2013

Discussion

We describe for the first time betatrophin concentrations in humans, and report that circulating concentrations of betatrophin are increased in type 1 diabetes in contrast with

ANGPTL8 & T2D

OPEN

Higher plasma betatrophin/ ANGPTL8 level in Type 2 Diabetes subjects does not correlate with blood glucose or insulin resistance

Received: 29 October 2014
Accepted: 11 May 2015
Published: 16 June 2015

Mohamed Abu-Farha[1], Jehad Abubaker[1], Irina Al-Khairi[1], Preethi Cherian[1], Fiona Noronha[2], Frank B. Hu[3], Kazem Behbehani[1,2] & Naser Elkum[4]

Recent reports investigating betatrophin link to T2D circulation showed contradictory data. A number of studies showed that betatrophin level was increased in T2D subjects[19–21] while, Gomez-Ambrosi *et al.* showed that betatrophin was reduced in T2D subjects[29]. In the current study, we showed that circu-

Increased Circulating Levels of Betatrophin in Newly Diagnosed Type 2 Diabetic Patients

Hao Hu,[1] Wenjun Sun,[1] Shuqin Yu,[1] Xiafei Hong,[1] Weiyun Qian,[1] Bingqian Tang,[1] Dong Wang,[1] Ling Yang,[1] Jifang Wang,[1] Caoming Mao,[1] Libin Zhou,[2] and Guoyue Yuan[1]

Diabetes Care 2014;37:2718–2722 | DOI: 10.2337/dc14-0602

CONCLUSIONS

Circulating concentrations of betatrophin are significantly increased in T2DM patients. Our results suggest that betatrophin may play a role in the pathogenesis of T2DM.

Endocrine Journal 2015, **62** (5), 417-421

ORIGINAL

Circulating betatrophin is elevated in patients with type 1 and type 2 diabetes

Hodaka Yamada, Tomoyuki Saito, Atsushi Aoki, Tomoko Asano, Masashi Yoshida, Aki Ikoma, Ikuyo Kusaka, Hideo Toyoshima, Masafumi Kakei and San-e Ishikawa

Division of Endocrinology and Metabolism, Jichi Medical University Saitama Medical Center, Saitama 330-8503 Japan

Increased Circulating Betatrophin Concentrations in Patients with Type 2 Diabetes

Daniel Espes,[1,2] Mats Martinell,[3] and Per-Ola Carlsson[1,2]

4. Discussion

The present work shows that plasma betatrophin concentrations in patients with type 2 diabetes are not subnormal, instead higher concentrations than in nondiabetic individuals were recorded. Therefore, although resistance to

Circulating Betatrophin Levels Are Increased in Patients With Type 2 Diabetes and Associated With Insulin Resistance

Xi Chen,* Puhan Lu,* Wentao He, Jianhua Zhang, Lei Liu, Yan Yang, Zhelong Liu, Junhui Xie, Shiying Shao, Tingting Du, Xianghui Su, Xinrong Zhou, Shuhong Hu, Gang Yuan, Muxun Zhang, Hong Zhang, Liegang Liu, Daowen Wang, and Xuefeng Yu

Conclusion: Circulating betatrophin levels are increased in patients with T2DM and associated with indexes of insulin resistance. (*J Clin Endocrinol Metab* 100: E96–E100, 2015)

Circulating Betatrophin Concentrations Are Decreased in Human Obesity and Type 2 Diabetes

Javier Gómez-Ambrosi, Eider Pascual, Victoria Catalán, Amaia Rodríguez, Beatriz Ramírez, Camilo Silva, María J. Gil, Javier Salvador, and Gema Frühbeck

In conclusion, our results show that serum betatrophin concentrations are decreased in obese subjects and are further reduced in parallel to the increase in insulin resistance. Moreover, serum betatrophin levels are markedly increased in women as compared to men, which could help to explain the increased risk of diabetes found in men. Further studies modulating betatrophin levels and activity, determining which are the pathophysiological regulators of betatrophin, together with the identification of the betatrophin receptor will undoubtedly help to elucidate the exact role of betatrophin in obesity and obesity-associated comorbidities such as T2D and dyslipidemia.

Abu-Farha et al[20,34]	Increased ANGPTL8 in obese people.	Increased ANGPTL8 in people with T2D.
Fu et al[37]	Increased ANGPTL8 level in obesity.	Increased ANGPTL8 level in people with T2D.
Gomez-Ambrosi et al[38]	Decreased ANGPTL8 level in obese people.	Decreased ANGPTL8 level in people with T2D.
Hu et al[39]	NA	Higher ANGPTL8 level in newly diagnosed people with T2D.

(47)

ANGPTL8

&

gestational diabetes mellitus

Evaluation of circulating betatrophin levels in gestational diabetes mellitus

Onur Erol[1], Hamit Yaşar Ellidağ[2], Hülya Ayık[1], Mustafa Kemal Özel[1], Aysel Uysal Derbent[1], and Necat Yılmaz[2]

[1]Department of Obstetrics and Gynecology and [2]Department of Biochemistry, Antalya Training and Research Hospital, Antalya, Turkey

In conclusion, we demonstrated that serum betatrophin levels were significantly higher in women with GDM compared to healthy pregnant controls. It is difficult to infer whether high betatrophin level is a cause or effect of GDM. Further studies are needed to clarify the significance and the underlying mechanisms of the increased betatrophin levels in GDM.

Betatrophin levels are increased in women with gestational diabetes mellitus compared to healthy pregnant controls

Thomas Ebert[1,2,*], Susan Kralisch[1,2,*], Ulrike Wurst[1,2], Ulrike Lössner[1,2], Jürgen Kratzsch[3], Matthias Blüher[1], Michael Stumvoll[1], Anke Tönjes[1,2] and Mathias Fasshauer[1,2]

In conclusion, women with GDM have significantly higher betatrophin levels as compared to healthy pregnant controls and GDM status positively predicts circulating betatrophin. Furthermore, *postpartum* levels are

RESEARCH ARTICLE

Circulating Betatrophin Is Strongly Increased in Pregnancy and Gestational Diabetes Mellitus

Lana Kosi Trebotic[1], Peter Klimek[3], Anita Thomas[1], Anna Fenzl[1], Karoline Leitner[1], Stefanie Springer[2], Florian W. Kiefer[1], Alexandra Kautzky-Willer[1]*

Conclusions/interpretation

Circulating betatrophin concentrations are dramatically increased in pregnancy and are significantly higher in GDM versus pregnant NGT. In the light of the previously reported role in lipid metabolism, betatrophin may represent a novel endocrine regulator of lipid alterations in pregnancy. However additional studies are needed to elucidate whether hormonal fac-

RESEARCH ARTICLE

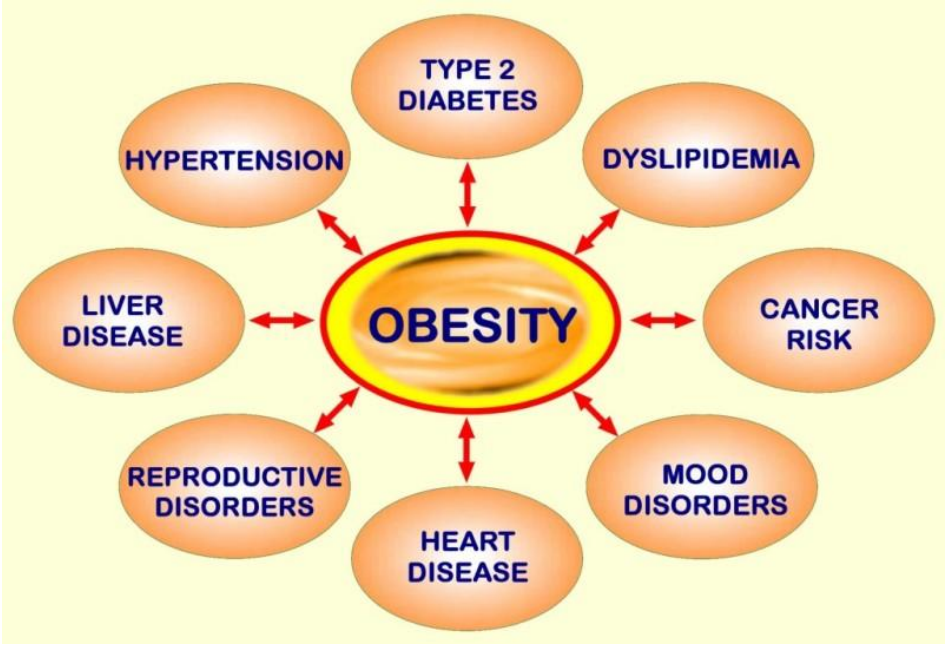
Increased Maternal and Cord Blood Betatrophin in Gestational Diabetes

Natalia Wawrusiewicz-Kurylonek[1], Beata Telejko[1], Mariusz Kuzmicki[2]*, Angelika Sobota[2], Danuta Lipinska[1], Justyna Pliszka[1], Beata Raczkowska[1], Pawel Kuc[3], Remigiusz Urban[3], Jacek Szamatowicz[2], Adam Kretowski[1], Piotr Laudanski[3], Maria Gorska[1]

Conclusions

Our results suggest that an increase in maternal and cord blood betatrophin might be a compensatory mechanism for enhanced insulin demand in GDM.


OBESITY


TYPE 2 DIABETES
HYPERTENSION
DYSLIPIDEMIA
LIVER DISEASE
OBESITY
CANCER RISK
REPRODUCTIVE DISORDERS
MOOD DISORDERS
HEART DISEASE


UNDERWEIGHT
HEALTHY WEIGHT
OVERWEIGHT
OBESE
BMI

Identification of RIFL, a novel adipocyte-enriched insulin target gene with a role in lipid metabolism

Gang Ren, Ji Young Kim, and Cynthia M. Smas

Department of Biochemistry and Cancer Biology and Center for Endocrine and Diabetes Research, University of Toledo College of Medicine, Toledo, Ohio

Submitted 16 February 2012; accepted in final form 7 May 2012

liver-secreted protein that impacts lipid metabolism. In summary, our data suggest that RIFL is an important new regulator of lipid metabolism.

RIFL has the potential to play an important role in adipocyte function and/or lipid metabolism in humans. Work in this

RIFL gene expression was increased in fat and liver of obese mice. RIFL expression was induced by insulin.[22]

Emerging roles of Lipasin as a critical lipid regulator

Ren Zhang[a,*], Abdul B. Abou-Samra[a,b]

[a] *Center for Molecular Medicine and Genetics, School of Medicine, Wayne State University, Detroit, MI 48201, USA*
[b] *Department of Medicine, Hamad Medical Corporation, Doha, Qatar*

ARTICLE INFO

Article history:
Received 29 January 2013
Available online 13 February 2013

ABSTRACT

Patients with metabolic syndrome are at high risk for developing atherosc
and diabetes. In addition to total cholesterol, LDL-C and HDL-C, elevated
increasingly recognized as an independent risk factor for cardiovascular dis

Expressions of Lipasin, ANGPTL3 and ANGPTL4 in response to various stimuli.

	Liver		WAT		BAT		
	Fasting	Obesity[a]	Fasting	Obesity	Fasting	Obesity	Cold
Lipasin	↓	↑	↓	↑	↓	↑	↑
ANGPTL4	↑	--	↑	--	↑	--	↓
ANGPTL3	--	↑	NA	NA	NA	NA	NA

RESEARCH ARTICLE

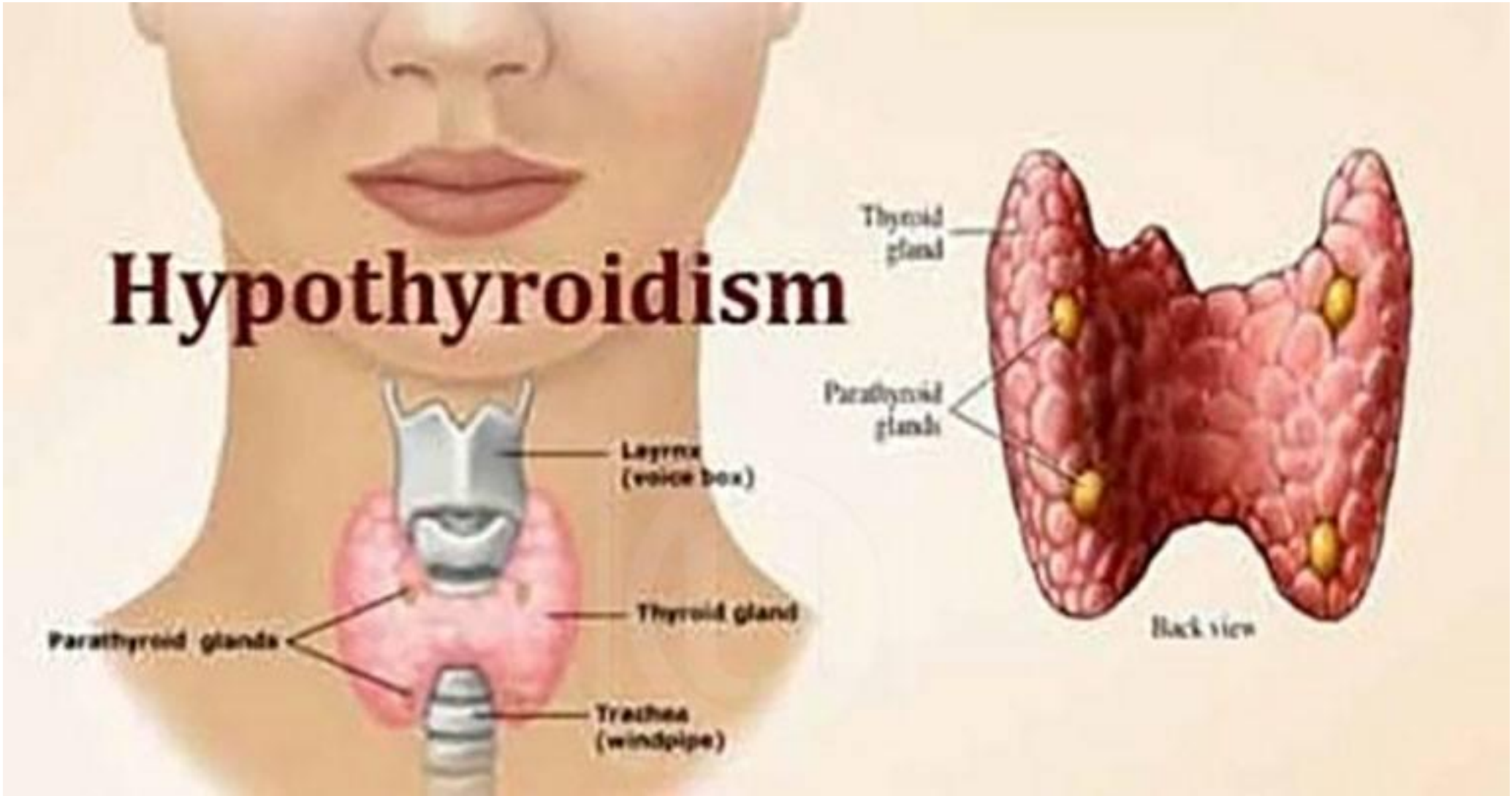
Circulating ANGPTL8/Betatrophin Is Increased in Obesity and Reduced after Exercise Training

Mohamed Abu-Farha[1]*, Devarajan Sriraman[2], Preethi Cherian[1], Irina AlKhairi[1], Naser Elkum[3], Kazem Behbehani[1,2], Jehad Abubaker[1]*

Conclusion

In conclusion, our data demonstrate that ANGPTL8 was increased in obesity and reduced after exercise training supporting the potential therapeutic benefit of reducing ANGPTL8.

ANGPTL8 & Hypothyroidism



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Volume 2016, Article ID 5090852, 6 pages
http://dx.doi.org/10.1155/2016/5090852

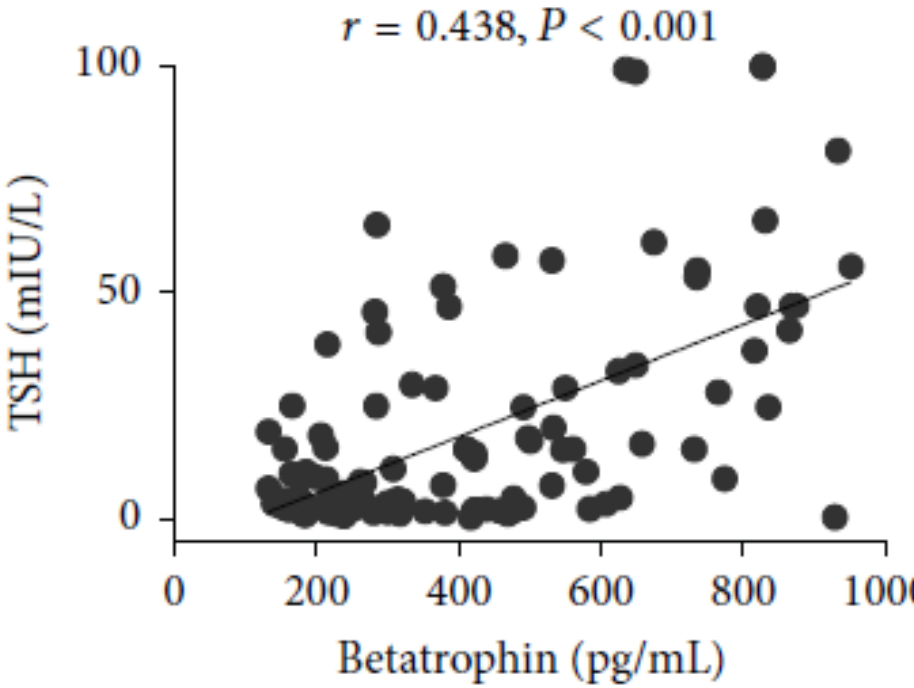
Hindawi

Research Article

Circulating Betatrophin Is Increased in Patients with Overt and Subclinical Hypothyroidism

Cheng Han,[1] Xinghai Xia,[1] Aihua Liu,[1] Xiaowen Zhang Xin Liu,[1] Jie Sun,[1] Xiaoguang Shi,[1] Zhongyan Shan,[1] ar

serum betatrophin level was increased in correlation with increased severity of hypothyroidism (with increased TSH and decreased FT4). Also, serum betatrophin concentrations were independently associated with TSH and TG.



ANGPTL8 & MetS

Interplay of atherogenic factors, protein intake and betatrophin levels in obese-metabolic syndrome patients treated with hypocaloric diets

Ana B. Crujeiras [1,3], Maria A Zulet [2,3], Itziar Abete [2,3], María Amil [1,3], Marcos C Carreira [1,3], J Alfredo Martínez [2,3], Felipe F Casanueva [1,3]

RESULTS. Betatrophin levels were higher in obese-metabolic syndrome patients than normal-weight subjects (1.24±0.43 ng/mL vs. 0.97±0.69 ng/mL, respectively, p=0.012), and levels were positively associated with body composition, metabolic parameters, leptin and irisin in all participants at baseline. Notably, low pre-intervention (wk0) betatrophin levels in obese patients were significantly associated with higher dietary-induced changes in atherogenic risk factors after 8 weeks. Moreover, protein intake, especially proteins from animal sources, was an independent determinant of betatrophin levels after dietary treatment (B=-0.27; p=0.012).

CONCLUSIONS. Betatrophin is elevated in obese patients with metabolic syndrome features and is associated with poorer nutritional outcomes of adiposity and dyslipidemia traits after a weight-loss program. Dietary protein intake could be a

Abu-Farha et al. Cardiovasc Diabetol (2016) 15:25
DOI 10.1186/s12933-016-0346-0

Cardiovascular Diabetology

ORIGINAL INVESTIGATION

Open Access

Circulating angiopoietin-like protein 8 (betatrophin) association with HsCRP and metabolic syndrome

Mohamed Abu-Farha[1*], Jehad Abubaker[1], Irina Al-Khairi[1], Preethi Cherian[1], Fiona Noronha[2], Sina Kavalakatt[1], Abdelkrim Khadir[1], Kazem Behbehani[2], Monira Alarouj[2], Abdullah Bennakhi[2] and Naser Elkum[3*]

Results: ANGPTL8 level was higher in subjects with MetS 1140.6 (171.9–11736.1) pg/mL compared to 710.5 (59.5–11597.2) pg/mL in the controls. Higher levels of ANGPTL8 were also observed with the sequential increase in the number of MetS components (p value = <0.0001). ANGPTL8 showed strong positive correlation with HsCRP ($r = 0.15$, p value = <0.0001). Stratifying the population into tertiles according to the level of HsCRP showed increased ANGPTL8 level at higher tertiles of HsCRP in the overall population (p value = <0.0001).A similar trend was also observed in MetS and non-MetS subjects as well as in non-obese and obese subjects. Finally, multiple logistic regression models adjusted for age, gender, ethnicity and HsCRP level showed that subjects in the highest tertiles of ANGPTL8 had higher odds of having MetS (odd ratio [OR] = 2.3, 95 % confidence interval [CI] = (1.6–3.1), p value <0.0001.

Conclusion: In this study we showed that ANGPTL8 is increased in subjects with MetS and it was significantly associated with HsCRP levels in different subgroups highlighting its potential role in metabolic and inflammatory pathways.

ANGPTL8
&
polycystic ovary syndrome

Assessment of circulating betatrophin concentrations in lean glucose-tolerant women with polycystic ovary syndrome

Onur Erol, Mustafa Kemal Özel, Hamit Yaşar Ellidağ, Tayfun Toptaş, Aysel Uysal Derbent & Necat Yılmaz

To cite this article: Onur Erol, Mustafa Kemal Özel, Hamit Yaşar Ellidağ, Tayfun Toptaş, Aysel Uysal Derbent & Necat Yılmaz (2017) Assessment of circulating betatrophin concentrations in lean glucose-tolerant women with polycystic ovary syndrome, Journal of Obstetrics and Gynaecology, 37:5, 633-638, DOI: 10.1080/01443615.2017.1286464

Therefore, we speculated that higher betatrophin levels in women with PCOS may be attributable to increases in the insulin resistance of such patients. However, we found no significant correlation between betatrophin concentrations and

Endocrine
July 2016, Volume 53, Issue 1, pp 271–279 | Cite as

Elevated circulating levels of betatrophin are associated with polycystic ovary syndrome

Authors | Authors and affiliations

Mehmet Calan, Ozgur Yilmaz, Tuncay Kume, Gokcen Unal Kocabas, Pinar Yesil Senses, Yasar Mehmet Senses, Muzaffer Temur, Ozlem Gursoy Calan

regression analyses showed that HOMA-IR, hs-CRP, and free-testosterone were independent factors influencing serum betatrophin levels. Betatrophin levels were increased in women with PCOS and were associated with insulin resistance, hs-CRP, and free-testosterone in these patients. Elevated betatrophin levels were found to increase the odds of having PCOS. Further research is needed to elucidate the physiologic and pathologic significance of our findings.

Elevated serum levels of betatrophin in patients with polycystic ovary syndrome and the influential factors

SONG Shumin, WANG Jia, GUO Chenghui, JIANG Tiejian

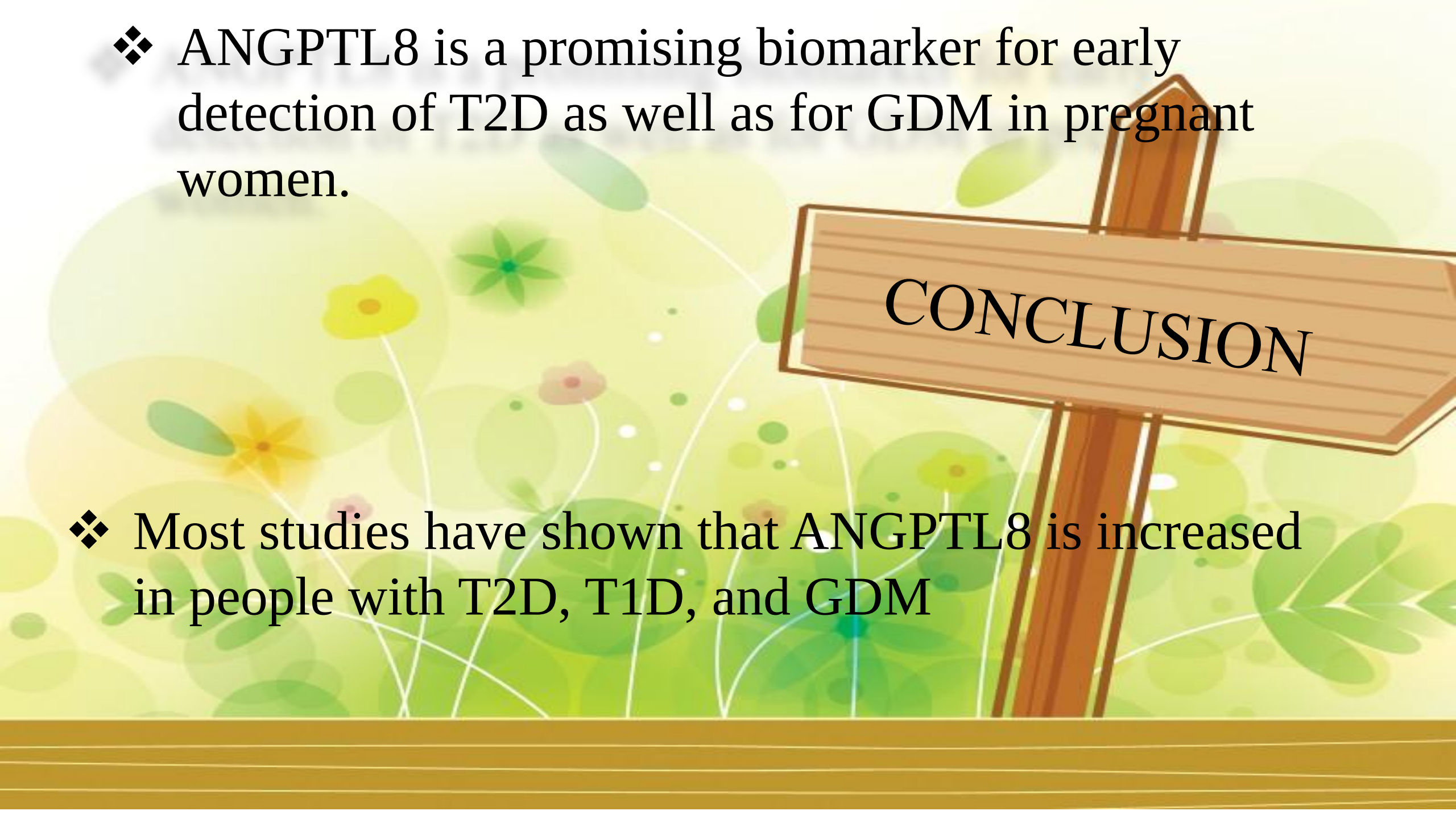
(Department of Endocrinology, Xiangya Hospital, Central South University, Changsha 410008, China)

ABSTRACT

Objective: To determine serum levels of betatrophin in patients with polycystic ovary syndrome (PCOS) and the influential factors.

Methods: A total of 100 PCOS patients were enrolled randomly as a PCOS group, and 40 age-matched healthy women were recruited as a normal control (NC) group. Primary clinical or biochemical parameters of the subjects were detected. The results were analyzed by SPSS 19.0.

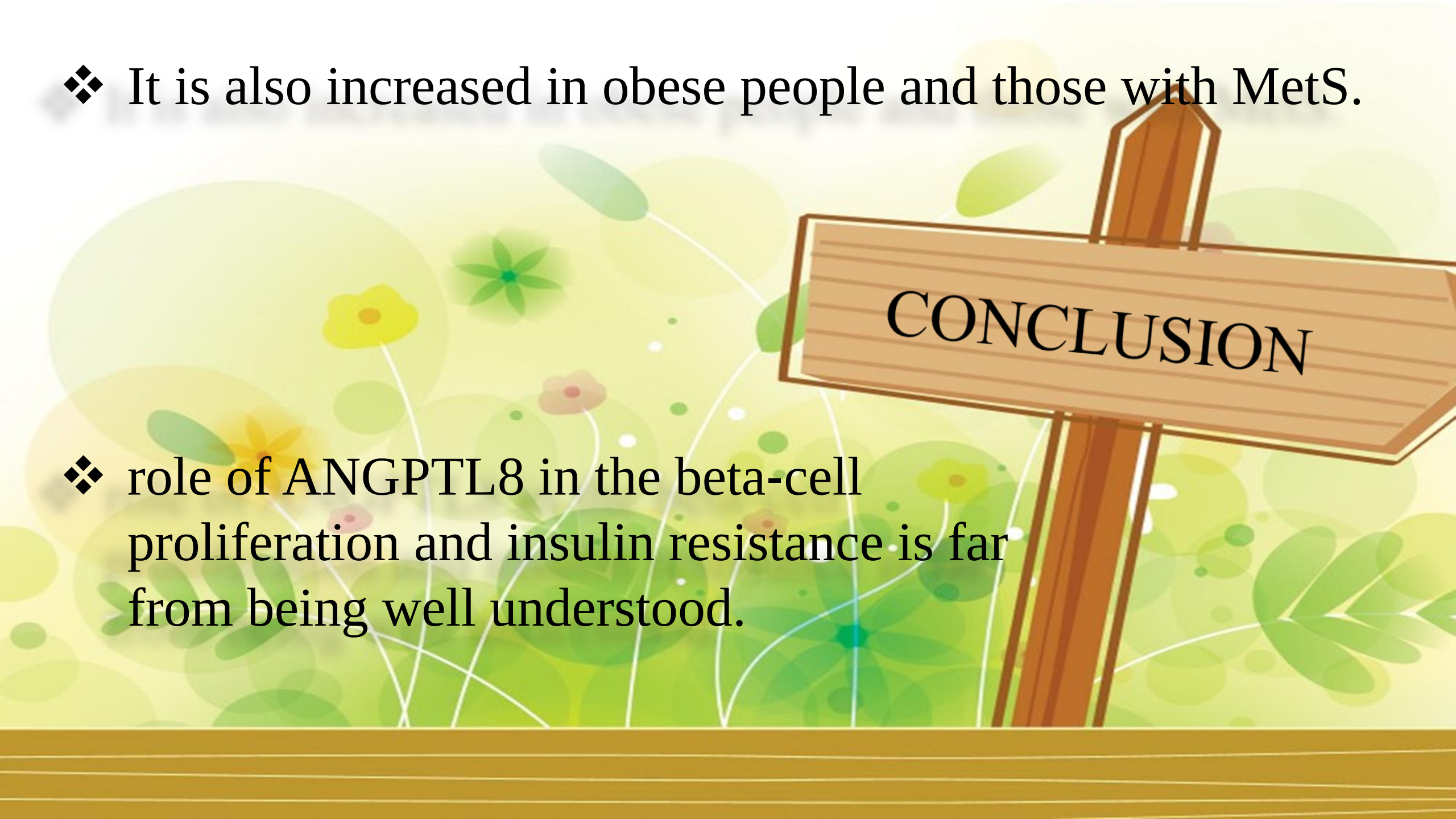
Results: Serum betatrophin levels were elevated in the PCOS group compared with the NC group. Serum betatrophin levels were positively correlated with age and Whole Body Insulin Sensitivity Index (WBISI),and negatively correlated with body mass index, fasting insulin(FINS), homeostatic model assessment insulin resistance (HOMA-IR) and homeostatic model assessment β cell



- ANGPTL8 is a promising biomarker for early detection of T2D as well as for GDM in pregnant women.

- Most studies have shown that ANGPTL8 is increased in people with T2D, T1D, and GDM

- It is also increased in obese people and those with MetS.



- role of ANGPTL8 in the beta-cell proliferation and insulin resistance is far from being well understood.

β-cell proliferation

T1D

T2D

gestational diabetes mellitus

obesity

Hypothyroidism

MetS

polycystic ovary syndrome

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Thank You for Attention